EXHIBIT R

PAIN MANAGEMENT

BEST PRACTICES

PAIN MANAGEMENT BEST PRACTICES INTER-AGENCY TASK FORCE REPORT

Updates, Gaps, Inconsistencies, and Recommendations

FINAL REPORT

Submitted by the:

Pain Management Best Practices Inter-Agency Task Force

Report Date:

May 9, 2019

Suggested Citation:

U.S. Department of Health and Human Services (2019, May). Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations. Retrieved from U. S. Department of Health and Human Services website: https://www.hhs.gov/ash/advisory-committees/pain/reports/index.html

GAPS AND RECOMMENDATIONS

GAP 1: There is a need for opioid prescribing guidelines for the aging population that provide the potential for increased risk of falls, cognitive impairment, respiratory depression, organ metabolism impairment, and age-related and non-age-related pain issues.

- **RECOMMENDATION 1A:** Develop pain management guidelines for older adults that address their unique risk factors. However, a risk factor of a medication should not necessarily be an automatic reason not to give this medication to an elderly patient. Clinicians must assess the risk versus benefit of using medications while considering other modalities in this patient population.
- **RECOMMENDATION 1B:** Consider using a multidisciplinary approach with nonpharmacologic emphasis given the increased risk of medication side effects in this population.
- **RECOMMENDATION 1C:** Establish appropriate pain management education for physicians and health care providers who treat older adults.

2.7.3 Patients with Cancer-Related Pain and Patients in Palliative Care

Cancer pain affects millions of Americans.[306,354] In addition, there are more than 14 million cancer survivors in the United States as a result of remarkable advances in cancer diagnosis and therapy. An estimated 40% of cancer survivors continue to experience persistent pain as a result of treatments such as surgery, chemotherapy, and radiation therapy. Persistent pain is also common and significant in patients with a limited prognosis, as often encountered in hospice and palliative care environments.[355]

GAPS AND RECOMMENDATIONS

GAP 1: These patient populations are frequently managed by practitioners who do not specialize in pain or palliative care. Many oncologists and primary care physicians are not trained to recognize or treat persistent pain associated with cancer or other chronic medical problems with limited prognosis.

- **RECOMMENDATION 1A:** Clinicians should assess and address pain at each patient encounter. Causes of pain such as recurrent disease, second malignancy, or late-onset treatment effects should be evaluated, treated, and monitored.

GAP 2: Patients with persistent pain associated with cancer and/or cancer treatment or other chronic medical problems with limited prognosis in palliative care often receive less optimal care with restricted treatment modalities.

- **RECOMMENDATION 2A:** When clinically indicated, use multimodal and multidisciplinary treatment as part of cancer-related pain management and palliative care.

2.7.4 Unique Issues Related to Pain Management in Women

Central to the unique issues women face in pain management are the differences between men and women with respect to pain sensitivity, response to pain medication, and predisposition to clinical pain conditions.[356] Data and recent literature suggest that women experience more pain than men, have greater sensitivities to painful stimuli compared with men, and report experiencing more intense pain.[357,358] In addition to the response to pain medication, there exist sex differences in the patterns of nonmedical use and abuse of prescription opioids.[359,360] Research has identified that women are more likely than men to misuse prescription opioids.[361] Furthermore, from 1999 to 2010, the percentage increase in opioid-related overdose deaths was greater in women than in men.[362] Finally, women face unique pain management challenges in the pregnancy and postpartum periods. To mitigate the heightened risk associated with pain management in these periods, it is important to emphasize the importance of obstetricians and gynecologists (OB-GYNs) on the multidisciplinary pain management team.

GAPS AND RECOMMENDATIONS

GAP 1: Women face unique challenges regarding their physical and mental health, interactions with the health care system, and roles in society. Women use the health care system as patients, caregivers, and family representatives and can be particularly affected by costs, access issues, and gender insensitivity from health care providers and staff. Several diseases associated with pain — in particular, chronic high-impact pain — have a higher prevalence in women or are sex specific, including endometriosis, musculoskeletal and orofacial pain, fibromyalgia, migraines, and abdominal and pelvic pain.

- **RECOMMENDATION 1A:** Increase research to elucidate further understanding of the mechanisms driving sex differences in pain responses and research of mechanism-based therapies that address those differences.
- **RECOMMENDATION 1B:** Raise awareness in the public and health care arenas to the unique challenges that women face during pregnancy and in the postpartum period, including various pain syndromes and psychosocial comorbidities.

GAP 2: Women may experience increased pain sensitivity. Of note, OB-GYNs may be one of the first health care providers a woman with pain encounters, yet they are not often included as part of a multidisciplinary care team.

- **RECOMMENDATION 2A:** Include OB-GYNs as part of multidisciplinary care teams because they are likely to play an important role in the treatment of pain for women.

2.7.5 Pregnancy

Managing pain in pregnant women is uniquely challenging because clinical decision making must account for the pregnant mother and the developing fetus.[363] Further complicating pain management in the peripartum period is the lack of CPGs for nonpharmacologic treatments that may decrease the potential adverse outcomes for newborns associated with opioid therapy, such as neonatal abstinence syndrome. Greater research into chronic pain management in pregnancy is needed.[364–366]

GAPS AND RECOMMENDATIONS

GAP 1: There is a need for evidence-based CPGs for the use of analgesics during pregnancy and the postpartum period.

- **RECOMMENDATION 1A:** Improve evidence for pain management of pregnant and postpartum women with greater research and innovation, in collaboration with the national specialty societies (the American College of Obstetricians and Gynecologists, neonatologists, obstetricians, perinatal pediatricians, and other specialists).
- **RECOMMENDATION 1B:** Counsel women of childbearing age on the risks of opioids and non-opioid medications in pregnancy, including risks to the fetus and newborns.

2.7.6 Chronic Relapsing Pain Conditions

Chronic pain with periods of remission and frequent relapses defines "chronic relapsing pain conditions." Examples of such conditions include various degenerative, inflammatory, immune-mediated, rheumatologic, and neurologic conditions such as MS, trigeminal neuralgia, Parkinson's disease, CRPS, porphyria, systemic lupus erythematosus, lumbar radicular pain, migraines, and cluster headaches. Acute pain flares on top of the chronic pain condition can be a common occurrence that may affect daily routines and overall functionality, resulting in additional morbidity and the need for comprehensive pain care.

REFERENCES

359. Back SE, Payne RL, Simpson AN, Brady KT. Gender and Prescription Opioids: Findings from the National Survey on Drug Use and Health. *Addict Behav*. 2010;35(11):1001-1007. doi:10.1016/j.addbeh.2010.06.018

360. Glerum K, Choo E. Gender and Prescription Opioid Abuse. American Medical Women's Association. https://www.amwa-doc.org/sghc/sghc-case-studies/gender-and-prescription-opioid-abuse/. Published 2015. Accessed October 10, 2018.

361. Green TC, Black R, Grimes Serrano JM, Budman SH, Butler SF. Typologies of prescription opioid use in a large sample of adults assessed for substance abuse treatment. *PloS One*. 2011;6(11):e27244. doi:10.1371/journal.pone.0027244

362. Centers for Disease Control and Prevention. Vital Signs: Overdoses of Prescription Opioid Pain Relievers and Other Drugs Among Women — United States, 1999–2010. Morbidity and Mortality Weekly Report. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6226a3.htm. Published July 5, 2013. Accessed October 10, 2018.

363. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain Off J Am Pain Soc*. 2009;10(2):113-130. doi:10.1016/j.jpain.2008.10.008

364. Shah S, Banh ET, Koury K, Bhatia G, Nandi R, Gulur P. Pain Management in Pregnancy: Multimodal Approaches. *Pain Res Treat*. 2015;2015. doi:10.1155/2015/987483

365. Hadi I, da Silva O, Natale R, Boyd D, Morley-Forster PK. Opioids in the parturient with chronic nonmalignant pain: a retrospective review. *J Opioid Manag*. 2006;2(1):31-34.

366. Ray-Griffith SL, Wendel MP, Stowe ZN, Magann EF. Chronic pain during pregnancy: a review of the literature. *Int J Womens Health*. 2018;10:153-164. doi:10.2147/IJWH.S151845

367. Kato GJ, Piel FB, Reid CD, et al. Sickle cell disease. *Nat Rev Dis Primer*. 2018;4:18010. doi:10.1038/nrdp.2018.10

368. Brousseau DC, Panepinto JA, Nimmer M, Hoffmann RG. The number of people with sickle-cell disease in the United States: national and state estimates. *Am J Hematol*. 2010;85(1):77-78. doi:10.1002/ajh.21570

369. Brousseau DC, Owens PL, Mosso AL, Panepinto JA, Steiner CA. Acute care utilization and rehospitalizations for sickle cell disease. *JAMA*. 2010;303(13):1288-1294. doi:10.1001/jama.2010.378

370. Lanzkron S, Carroll CP, Haywood CJ. The burden of emergency department use for sickle-cell disease: an analysis of the national emergency department sample database. *Am J Hematol*. 2010;85(10):797-799. doi:10.1002/ajh.21807

371. Dampier C, Palermo TM, Darbari DS, Hassell K, Smith W, Zempsky W. AAPT Diagnostic Criteria for Chronic Sickle Cell Disease Pain. *J Pain Off J Am Pain Soc*. 2017;18(5):490-498. doi:10.1016/j.jpain.2016.12.016

372. Sil S, Cohen LL, Dampier C. Psychosocial and Functional Outcomes in Youth With Chronic Sickle Cell Pain. *Clin J Pain*. 2016;32(6):527-533. doi:10.1097/AJP.0000000000000289

373. Smith WR, Penberthy LT, Bovbjerg VE, et al. Daily assessment of pain in adults with sickle cell disease. *Ann Intern Med*. 2008;148(2):94-101.

374. Brandow AM, Zappia KJ, Stucky CL. Sickle cell disease: a natural model of acute and chronic pain. *Pain*. 2017;158 Suppl 1:S79-S84. doi:10.1097/j.pain.0000000000000824

375. Darbari DS, Ballas SK, Clauw DJ. Thinking beyond sickling to better understand pain in sickle cell disease. *Eur J Haematol*. 2014;93(2):89-95. doi:10.1111/ejh.12340

376. Miller AC, Gladwin MT. Pulmonary complications of sickle cell disease. *Am J Respir Crit Care Med*. 2012;185(11):1154-1165. doi:10.1164/rccm.201111-2082CI

377. Vanderhave KL, Perkins CA, Scannell B, Brighton BK. Orthopaedic Manifestations of Sickle Cell Disease. *J Am Acad Orthop Surg*. 2018;26(3):94-101. doi:10.5435/JAAOS-D-16-00255

378. Brandow AM, DeBaun MR. Key Components of Pain Management for Children and Adults with Sickle Cell Disease. *Hematol Oncol Clin North Am*. 2018;32(3):535-550. doi:10.1016/j.hoc.2018.01.014

379. Bulgin D, Tanabe P, Jenerette C. Stigma of Sickle Cell Disease: A Systematic Review. *Issues Ment Health Nurs*. 2018;39(8):675-686. doi:10.1080/01612840.2018.1443530

MARCH OF DIMES

CARING FOR A BABY WITH NAS

WHAT ARE THE SIGNS AND SYMPTOMS OF NAS?

Babies born with neonatal abstinence syndrome (also called NAS) can have health problems at birth and may need treatment in a hospital. They may have low birthweight and jaundice (when the eyes and skin look yellow). They also may have signs and symptoms like:

- Problems with breathing, feeding and sleeping
- Being fussy, crying a lot and having a high-pitched cry
- Body shakes and seizures
- Fever

As they grow older, children who had NAS may have problems with speech, language and learning. They may need early intervention services to help them learn to walk, talk and interact with others.

NAS is a group of conditions caused when a baby withdraws from certain drugs he's exposed to in the womb before birth. NAS most often happens when a baby's mother takes opioids during pregnancy.

CARING FOR A BABY WITH NAS

1. After birth, your baby may need to stay in the hospital for treatment.
2. Make sure your baby gets ongoing care from a health care provider. Don't try to treat NAS on your own.
3. Try these things to help calm your baby:
   - Keep your baby's room quiet and the lights dim.
   - Give your baby skin-to-skin care. Put your baby only in a diaper and lay him on your bare chest.
   - If possible, breastfeed your baby.
   - Read to your baby.
4. Always put your baby on his back to sleep to reduce the risk of sudden infant death syndrome (also called SIDS).
5. If you're worried about your baby's development, tell her provider. Ask about early intervention services. To find services, visit: cdc.gov/ncbddd/actearly

MARCHOFDIMES.ORG/NAS